COVID-19 vaccination rate and safety profile in a multicentre Italian population affected by mixed cryoglobulinaemic vasculitis

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Abstract

Objective

Mixed cryoglobulinaemic vasculitis (MCV) is an immune-complex-mediated systemic vasculitis characterised by heterogeneous clinical manifestations mainly involving lymphatic system, skin, kidney and peripheral nervous system. Although MCV patients have been included in priority programmes for vaccination against SARS-CoV-2 in Italy, limited information is available for these patients. The aims of this multicentre Italian study were to investigate SARS-CoV-2 vaccination rate in MCV patients and its safety profile.

Methods

All MCV patients referring to participating centres were assessed with an interview-based survey about vaccination, reasons for not getting vaccinated, adverse events (AE), and disease flares within a month after vaccination.

Results

A total of 416 patients were included in the study. Among participants, 7.7% did not get vaccinated, mainly for fear related to vaccine side-effects (50%) or medical decision (18.8%). They were more frequently treated with chronic glucocorticoids or rituximab (p=0.049 and p=0.043, respectively). Mild and self-limiting AE were recorded in 31.7% of cases, while post-vaccination vasculitis flares were observed in 5.3% of subjects. Disease relapses were mainly observed in patients with peripheral neuropathy or skin vasculitis (40% and 25%, respectively).

Conclusion

Vaccination against SARS-CoV-2 has been performed in a high percentage of MCV patients with encouraging safety profile. Vasculitis flares rate was in line with that observed for other autoimmune diseases, despite patients with purpura or peripheral neuropathy seem to be at risk for symptoms' exacerbation. Patients' hesitancy, rituximab and glucocorticoids treatment were the main reasons for delaying vaccination.

Key words

vasculitis, cryoglobulinaemia, SARS-CoV-2 vaccine

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Introduction

Mixed cryoglobulinaemic vasculitis (MCV) is an immune-complex-mediated systemic vasculitis involving small-medium-sized vessels with variable onset and severity, characterised by heterogeneous clinical manifestations mainly involving skin, kidney, peripheral nerves, and lymphatic system (1).

The immune system of MCV patients is affected by the disease *per se*, by the commonly prescribed immunosuppressive drugs and by the several MCV-associated comorbidities, which directly impact the response to infectious disease and vaccines. For this reason, MCV patients are supposed to have an increased risk of a more severe course of SARS-Coronavirus 2 (SARS-CoV-2) disease (COVID-19) (2), including hospitalisation and death; therefore, these subjects have been included in priority programs for vaccination against SARS-CoV-2 in Italy (3, 4).

Reassuring safety data emerged from the EULAR Coronavirus Vaccine physician-reported registry (COVAX) (5); however, a significant proportion of patients with autoimmune diseases included in another study reported unwillingness to get vaccinated against SARS-CoV-2, due to concerns about the lack of safety data in these patients, fear of side effects and disease flare (6). These troubles partially arise from the exclusion of patients with immune-mediated inflammatory diseases from SARS-CoV-2 vaccine clinical development programmes (5, 6).

In order to provide an expert position on this issue, the multidisciplinary task-force of the Italian Group for the Study of Cryoglobulinaemia (GISC) produced provisional recommendations regarding SARS-CoV-2 vaccination in MCV patients (3), but real-life data about SARS-CoV-2 vaccination rate and safety profile are still lacking in MCV patients.

The primary outcome of this multicentre cross-sectional study was to evaluate the SARS-CoV-2 vaccination rate in a cohort of Italian MCV patients. Secondary outcomes were to explore reasons for missing vaccination and to assess safety profile, including both adverse events (AE) and MCV flares.

Patients and methods

A multicentre cross-sectional study was conducted in 12 Italian centres with expertise in the management of MCV.

Consecutive patients that satisfied the preliminary classification criteria for MCV were enrolled between November 15th and December 15th (1); subjects with MCV secondary to lymphoproliferative disorders or connective tissue diseases were excluded from the study (1).

A careful assessment about SARS-CoV2 vaccination status was conducted for each subject, including the type of SARS-CoV2 vaccine (mRNA or adenovirus vector vaccine) and possible AEs classified according to FDA Toxicity Grading Scale for preventive vaccine clinical trials (7).

AEs were defined as short-term if occurred within 48 hours after SARS-CoV2 vaccination respectively, while MCV flare was defined related to vaccination if occurred within one month. Other AEs, appearing within a month from vaccination, were also recorded.

Both clinical and laboratory parameters were retrospectively reviewed and collected with reference to the time of vaccination or supposed decision to decline. Clinical features of MCV were reported, including cutaneous, renal and neurological manifestations. Furthermore, among laboratory parameters at baseline, we included history of hepatitis C virus (HCV), rheumatoid factor (RF), C3 and C4 fractions of complement, detection and characterisation of cryoglobulins (II or III type). Immunosuppressive therapies, namely rituximab, azathioprine, methotrexate, cyclosporin A, mycophenolate mofetil, cyclophosphamide, were also evaluated; steroid therapy was reported irrespective of the dose (4, 8, 9). Vasculitis flare was defined as the onset of a new organ involvement or worsening of the autoimmune disease within a month from the vaccination (10).

Statistical analysis

Baseline variables were expressed as percentages or median and interquartile ranges (IQR). Analyses were made using SAS software v. 9.2 (SAS Institute Inc., Cary, NC, USA), with a *p*-value

Table I. Clinico-serologic features of mixed cryoglobulinaemic patients according to the vaccination status.

	Total population 416 pts	Vaccinated pts 380 pts 92.3%	Unvaccinated pts 13 pts 7.7%	*p*-value
Males/females	133 (32%) / 283 (68%)	127 (95.5%) / 257 (90.8%)	6 (4.5%) / 26 (9.2%)	0.115
Mean age (years ± SD)	70.42 ± 11.75	70.94 ± 11.37	64.25 ± 14.42	**0.015**
Cryoglobulins type II (303)*	224 (73.9%)	207 (92.4%)	17 (7.6%)	0.806
Hepatitis C antibodies positivity	289 (69.6%)	274 (94.8%)	15 (5.2%)	**0.008**
Reduction of C4 (319)*	109 (34.2%)	95 (87.2%)	14 (12.8%)	0.231
Rheumatoid factor + (307)*	179 (58.3%)	157 (87.7%)	22 (12.3%)	0.178
Active vasculitis (*)	107 (27.2%)	104 (27.4%)	3 (23%)	1
Vasculic manifestations				
Skin purpura	28 (8.6%)	25 (8%)	3 (27.3%)	0.2
Peripheral neuropathy	40 (12.3%)	40 (12.8%)	0	0.2
Active glomerulonephritis	19 (5.9%)	17 (5.4%)	2 (18.2%)	0.2
Multiple manifestations	15 (4.6%)	15 (4.8%)	0	0.2
GC therapy	75 (18.1%)	65 (17%)	10 (32.3%)	**0.049**
RTX within 6 months	29 (7%)	24 (6.27%)	5 (17.2%)	**0.043**
Vaccine type				
Comirnaty-BioNTech/Pfizer		306 (80.5%)	-	
Spikevax/Moderna		34 (8.9%)	-	
Vaxzeviria-Oxford/Astrazeneca		29 (7.6%)	-	
Janssen-Johnson&Johns*on*		5 (1.3%)	-	
Reason for missed vaccination				0.533
Fear	-		16 (50%)	
Medical contraindication		-	6 (18.8%)	
Other		-	10 (31.3%)	

Data are reported as number (%). *the number in brackets indicates the number of patients for which data are available.
GC: glucocorticoids; RTX: rituximab.

<0.05 considered to be statistically significant. The differences between continuous variables were analysed using the Mann-Whitney nonparametric test. The chi-squared test, or Fisher's exact test when appropriated, was used for categorical variables (absolute numbers and percentages) regarding baseline characteristics.

Results

A total of 416 patients (68% females and 32% males, with a mean age of 70.4±11.7 years) were included in the study. Clinical, serological and therapeutic features are reported in Table I.

The large majority of MCV patients received the SARS-CoV2 vaccination (92.3%); mRNA vaccines were administered in most cases (Comirnaty 80.5%; Spikevax 8.9%), while six subjects (1.44%) underwent heterologous vaccination (usually Astra-Zeneca-Comirnaty) (Table I).

Thirteen patients (7.7%) did not get vaccinated, mainly for fear related to vaccine side-effects (50%) or medical decision (18.8%). Fear of AEs was the main cause for declining vaccination in female patients, while, for males, a prevalent cause did not emerge from the analysis.

No difference in vaccination rate was detected between patients with active and inactive vasculitis at the time of vaccination (Table I).

With regard to ongoing therapies, unvaccinated subjects were more frequently treated with chronic glucocorticoid therapy and/or rituximab (p=0.049 and p=0.043, respectively) (Table I). No significant associations were observed between other immunosuppressive therapies and vaccination rate; in particular, 2 patients were treated with cyclophosphamide, 2 with mycophenolate mofetil, 4 with azathioprine, and one subject with tacrolimus.

Table II reports frequency and characteristics of AE. Short-term, mainly mild and self-limiting (grade 1) AEs were recorded in 21.4% of patients. The most frequently reported were: asthenia (57, 13.7%), arthralgia (44, 10.6%) and hyperpyrexia higher than 37.5°C (29, 7%). Notably, short-term AEs were more commonly observed in female patients (p=0.015).

Post-vaccination vasculitis flares were observed in 5.3% of cases, especially in patients with ongoing glucocorticoid therapy (p=0.04). Disease relapses were mostly characterised by worsening of previous manifestations of MCV, and rapidly improved with a temporary increase of the ongoing treatment.

Furthermore, short-term AEs were less frequent in patients with active MCV (p=0.006); on the contrary, in this group of patients, a relapse of purpura was reported in 25% of the cases (p=0.004). Accordingly, patients presenting with peripheral neuropathy experienced a post-vaccination symptomatic neurological worsening in 17.5% of the cases (p=0.029), even without vasculitis flare, which occurred in 3 cases (7.5% of patients with peripheral neuropathy, p=0.45) (Table II).

No significant associations were observed between AEs and other features, such as age, type of SARS-CoV-2 vaccination, clinical or serological characteristics of disease.

Discussion

MCV is a rare vasculitis and its incidence and prevalence have significantly decreased in the last years, accordingly with HCV epidemiology.

Table II. Adverse events in cryobulinaemic vasculitis patients after anti-SARS-CoV-2 vaccination.

	AEs within 48 hours*	*p*	Arthralgias	*p*	Vasculitis flares within 30 days	*p*	Other AEs within 30 days	*p*
Total	89,21.4%				22,5.3%		33,8%	
Active *vs*. non-active vasculitis	13.1% *vs*. 25.9%	**0.006**	9.3 *vs*. 11.9%	0.591	7.5% *vs*. 4.9%	0.329	30.3% *vs*. 69.7%	0.686
RF positive *vs*. negative	19.6 *vs*. 33.6%	**0.008**	12.3% *vs*. 14.8%	0.61	7.3 *vs*. 3.1%	0.136	70% *vs*. 30%	0.242
GC treatment + *vs*. -	26.7% *vs*. 20.4%	0.276	14.7% *vs*. 9.7%	0.216	10.7% *vs*. 4.1%	**0.04**	25% *vs*. 75%	0.338
Purpura	25%	0.635	21.4%	0.101	14.3%	0.052	25%	**0.004**
Neuropathy	40%	**0.004**	15%	0.413	7.5%	0.458	17.5%	**0.029**
Gender (male *vs*. female)	14.3% *vs*. 24.7%	**0.015**	6% *vs*. 12.7%	**0.041**	3.8% *vs*. 6%	0.482	3.8% *vs*. 9.9%	**0.033**
RTX within 6 months	20.7%	1	13.8%	0.52	3.4%	1	0%	0.151

Data are reported as number (%).
GC: glucocorticoids; RTX: rituximab; AEs: adverse events; RF: rheumatoid factor.
*Headache, myalgia, local reaction, lymphadenomegaly, dizziness, dermatitis, nausea.

Although many studies have investigated the effects of vaccines in patients with autoimmune inflammatory systemic diseases, data on MCV patients are lacking. In particular, during the SARS-CoV-2 pandemic, many scientific societies have explored the unwillingness of rheumatic patients towards vaccination and their possible AEs, but only few studies have investigated the effect of SARS-CoV-2 vaccines in patients with MCV, both in terms of immunogenicity and AEs (11). To the best of our knowledge, this is the first large study exploring these aspects. Interestingly, our results are quite comparable to those conducted in patients affected with other autoimmune inflammatory systemic diseases (12). In particular, the rate of disease flares following vaccination is slightly higher than that observed in the COVAX study on patients affected by vasculitis (5.3% *vs*. 3.2%) (5). However, a careful monitoring should be reserved to subjects with purpura or peripheral neuropathy, given the mild increased risk of symptoms worsening.

Most disease flares were mild and rapidly controlled by a temporary increase of immunosuppressive therapy. However, we cannot exclude possible long-term re-exacerbations of MCV and only specific studies will be able to address this point. Furthermore, we cannot exclude, in patients with a relapse of MCV manifestations, that the main cause of the relapse was a possible reduction of immunosuppressive treatment before vaccination rather than vaccination itself.

Many patients underwent mRNA vaccination according to local national guidelines, while heterologous vaccination was performed only in a small percentage of patients, showing a good safety profile.

Reasons for delaying vaccination are different among patients and physicians. For patients, fear of side effects is one of the main reasons for declining vaccination. On the other side, for physicians, ongoing treatments, in particular rituximab and glucocorticoids, are the major cause for postposing vaccination, while disease activity did not change the decision to vaccinate. In this regard, according to current guidelines, vaccination should ideally be performed when the autoimmune disease is quiescent, but this is not always possible during a pandemic and the risk/benefit profile should be discussed case by case (3, 4).

Rituximab is a milestone for the treatment of MCV. Considering the risk of a reduced efficacy of vaccines related to this drug, anti-SARS-CoV-2 vaccination should be concluded 2-4 weeks before rituximab or 5–6 months after the last treatment course (3, 13). However, if severe or life-threatening manifestations of MCV are present, priority should be given to the treatment of the vasculitis. In this case, vaccination should be always taken into account, evaluating case by case the ratio between a possible reduction in vaccine efficacy and the risk of an infection by SARS-CoV-2 (3). Except for selected cases, current recommendations suggest to always consider vaccination (3).

Finally, despite the known negative effect of high dose glucocorticoids (≥ 20 mg of prednisone daily) on vaccine efficacy (9), limited data are available on the possible effect of long-term low-dose glucocorticoid therapy. This lack of knowledge could have influenced the reduced rate of vaccination in patients taking glucocorticoids. In fact, the reduction of vaccination rate in this subgroup of patients was independent by the glucocorticoids dose and the MCV disease activity.

In conclusion, despite the higher rate of disease flare in MCV patients compared to other autoimmune systemic inflammatory diseases (5), vaccination should be preferably proposed, considering the high risk for severe COVID-19 and the overall frailty of these subjects.

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References

1. DE VITA S, SOLDANO F, ISOLA M *et al*.: Preliminary classification criteria for the cryoglobulinaemic vasculitis. *Ann Rheum Dis* 2011; 70: 1183-90. https://doi.org/10.1136/ard.2011.150755
2. STRANGFELD A, SCHÄFER M, GIANFRANCESCO MA *et al*.: Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis*

2021; 80: 930-42. https://doi.org/10.1136/annrheumdis-2020-219498
3. SCARPATO S, SEBASTIANI M, QUARTUCCIO L *et al*.: Provisional recommendations for SARS-CoV-2 vaccination in patients with cryoglobulinaemic vasculitis. *Clin Exp Rheumatol* 2021; 39 (Suppl. 129): S149-54. https://doi.org/10.55563/clinexprheumatol/2v6v5j
4. BUGATTI S, BALDUZZI S, DE STEFANO L *et al*.: Correspondence on 'EULAR December 2020 viewpoints on SARS-CoV-2 vaccination in patients with RMDs'. *Ann Rheum Dis* 2021; 80: e156. https://doi.org/10.1136/annrheumdis-2021-220541
5. MACHADO PM, LAWSON-TOVEY S, STRANGFELD A *et al*.: Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry. *Ann Rheum Dis* 2022; 81: 695-709. https://doi.org/10.1136/annrheumdis-2021-221490
6. SEN P, GUPTA L, LILLEKER JB *et al*.: COVID-19 vaccination in autoimmune disease (COVAD) survey protocol. *Rheumatol Int* 2022; 42: 23-9. https://doi.org/10.1007/s00296-021-05046-4
7. Food and Drug Administration (FDA) United States. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. 2019. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/toxicity-grading-scale-healthy-adult-and-adolescent-volunteers-enrolled-preventive-vaccine-clinical
8. Società Italiana Reumatologia (SIR) Italy. Vaccinazioni nelle malattie reumatologiche: sicurezza ed efficacia. 2020. Available from: https://www.reumatologia.it/obj/files/covid19/DPL_VACCINI_2020_DEF.pdf
9. Centers for Disease Control and Prevention (CDC). Advisory committee on Immunization Practices (ACIP) Altered Immunocompetence Guidelines for Immunizations. 2022. Available from: https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html
10. DESBOIS AC, BIARD L, SÈNE D *et al*.: Rituximab-associated vasculitis flare: incidence, predictors, and outcome. *J Rheumatol* 2020; 47: 896-902. https://doi.org/10.3899/jrheum.190076
11. FERRI C, URSINI F, GRAGNANI L *et al*.: Impaired immunogenicity to COVID-19 vaccines in autoimmune systemic diseases. High prevalence of non-response in different patients' subgroups. *J Autoimmun* 2021; 125: 102744. https://doi.org/10.1016/j.jaut.2021.102744
12. VISENTINI M, GRAGNANI L, SANTINI SA *et al*.: Flares of mixed cryoglobulinaemia vasculitis after vaccination against SARS-CoV-2. *Ann Rheum Dis* 2022; 81: 441-3. https://doi.org/10.1136/annrheumdis-2021-221248
13. BENUCCI M, INFANTINO M, MAROTTO D, ARDIZZONE S, MANFREDI M, SARZI-PUTTINI P: Vaccination against SARS-CoV-2 in patients with rheumatic diseases: doubts and perspectives. *Clin Exp Rheumatol* 2021; 39: 196-202. https://doi.org/10.55563/clinexprheumatol/7afn90